REMARKS

According to the Office Action of April 4, 2008, claims 18-28 have been examined on their merits, and have been rejected. Claims 29-33 have been withdrawn by the Examiner as directed to non-elected subject matter. Particularly, the Office Action asserts at least one of the following rejections against each claim: (1) under 35 U.S.C. § 112, second paragraph, (2) under 35 U.S.C. § 112, first paragraph; and (3) under 35 U.S.C. § 103. Applicants have amended claim 18, cancelled claim 28, and added new claim 34. New claim 34 is directed to the method recited in claim 18, wherein the estrogenic component is administered orally. No new matter has been added by virtue of these amendments.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 28 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Since claim 28 has been cancelled, this rejection is now moot.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 18-28 are rejected under 35 U.S.C. §112, first paragraph, as not being enabled by the specification. Specifically, the Office Action contends that the specification enables the treatment of an immune mediated disease as defined in claim 18, but does not reasonably provide enablement for prophylactically treating such diseases.[1]

On page 7, the Office Action acknowledges that the specification enables the claimed invention with regard to treating an immune mediated disease. However, on page 10, the Office Action contends that "currently there is no known method that can cure or truly prophylactically treat the immune mediated diseases ... by employing a single therapeutic estrogenic agent because the causes of these diseases are either still unknown or derived from diverse factors," and therefore the claims are not enabled with respect to prophylactically treating the recited diseases.

[1] Office Action of April 4, 2008 at page 7.

The word "prophylaxis", which is Greek for "to guard or prevent beforehand", is defined as any medical or public health procedure whose purpose is to prevent, rather than treat or cure, disease.[2] Roughly, prophylactic measures are divided between *primary* prophylaxis (to prevent the development of a disease) and *secondary* prophylaxis (whereby the disease has already developed and the patient is protected against worsening of this process).

When asserting an enablement rejection, the Patent Office bears the burden of setting forth a reasonable explanation as to why it believes that the claims are not enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993); *In re Stoughton*, No. 2005-2235, App. No. 09/038,894, 2006 WL 1665412 at *4 (BPAI 2006). Precise predictability is not the standard to employ. *Ex parte Corpet*, No. 2004-1790, App. No. 09/836,971, 2004 WL 2733634 (BPAI 2004).

In *Corpet*, the examiner rejected claim 12 as not enabled by the specification. 2004 WL 2733634 at *1. Claim 12 recited "[a] method of preventing colon or rectum cancer comprising administering to a mammal a therapeutically effective amount of a non-fermented osmotic polyol laxative." *Id.* The rationale for rejecting claim 12 was based on the argument

> that the recitation of preventing "extend[s] the treatment to those patients in which rectal and colon cancers may occur at any point of time in [the] future." [Citation omitted.] With respect to the state of the art, the examiner apparently recognizes that "[t]he state of the art recognizes that increased intake of dietary fibers contribute to the increased bowel movements and thus result in lowering the risk of colon cancers," but asserts that "the art does not teach or recognize a complete prevention of the above claimed cancers." [Citation omitted.] Finally, with respect to guidance of the specification and examples, the examiner focuses on the lack of teaching of an understanding of when the cancer may occur.

Id. The Board determined that the examiner's rationale required "precise predictability as to the time when the colon or rectal cancer will appear, and also appears to require 100% prevention. That is not, however, a requirement under 35 U.S.C. § 112, first paragraph." *Id.* at *2. Due to this flawed rationale, the Board held that the examiner failed to meet his burden and reversed the rejection. *Id.* at *3.

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[2] WIKIPEDIA (http://en.wikipedia.org/wiki/Prophylaxis).

The Board reversed a similar rejection in *In re Goldenberg*, App No. 08/183,381, 2002 WL 31105508 (BPAI 2002). In *Goldenberg*, the examiner argued that "'[a]pplicant broadly claims an anti-idiotype vaccine to prevent cancer, AIDS and malaria, but the specification fails to enable the vaccine(s) and effectively teach how to make and/or use said vaccines to achieve this.'" *Id.* at *3. The Board held that this "failed to provide the evidence necessary to demonstrate that appellants' disclosure does not enable their claimed invention." *Id.* at *4. Like *Corpet*, the Board in *Goldenberg* reversed the rejection because the examiner required 100% predictability, which is not the standard for enablement.

These cases establish that claims directed to preventing or prophylactically treating a disease can be enabled by a specification. Thus, there is no *per se* bar against claims directed to prophylactically treating a disease. Instead, there must be reasonable explanation why one of ordinary skill in the art would not be able to practice the invention without undue experimentation.

The Office Action contends that "[o]ne of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and ***accurately determine*** whether said estrogenic compound and corresponding method of the instant application does in fact effectively and prophylactically treat all the claimed immune mediated disorders."[3] This rationale is akin to those used in *Corpet* and *Goldenberg*. Like *Corpet* and *Goldenberg*, this rejection is improperly premised on requiring precise predictability. Since precise predictability is not the standard, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Moreover, the Office Action contends that since the biological mechanisms that lead to multiple sclerosis and rheumatoid arthritis are not fully understood, the claims directed to methods of treating these diseases by administering an estrogenic component are not enabled.[4] Specifically, the Office Action states that "there is no known method that can cure or truly prophylactically treat the immune mediated diseases ... by employing a single therapeutic

[3] Emphasis added; Office Action at page 11.

[4] Office Action at pages 9-10.

estrogen because the causes of these diseases are still unknown and derived from diverse factors." This rationale suggests that the Patent Office will not issue a patent for any cure or prophylactic treatment unless all causes of the disease are known. However, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), quoting *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989). Thus, it is immaterial that the causes of the recited diseases are not known.

The Office Action also contends that the specification does not provide examples for prophylactically treating multiple sclerosis or arthritis. To the contrary, the specification provides examples similar to the ones provided in *Corpet*. In *Corpet*, the specification provided studies on rats. 2004 WL 2733634 at *2. The examiner argued that "'prevention is related to factors such as the length of time the tumor takes to manifest, type of animal being studied, etc." Examiner's Answer, page 8.'" *Id.* The Board found that this rationale required absolute predictability. *Id.* Since this is not the standard, the rejection was reversed. *Id.* at 3. Similarly, the instant specification provides examples that demonstrate that the recited invention prevents animals from developing an experimental autoimmune encephalomyelitis ("EAE") relapse (example 6) and that it suppresses the development of arthritis (example 8). Additionally, the examples establish that symptoms of EAE (examples 6 and 7) and arthritis (examples 8 and 9) were alleviated. From these examples, one of ordinary skill in the art would induce that the recited disease can be prophylactically treated by the recited invention.

For these reasons, it is respectfully requested that this rejection be reconsidered and withdrawn.

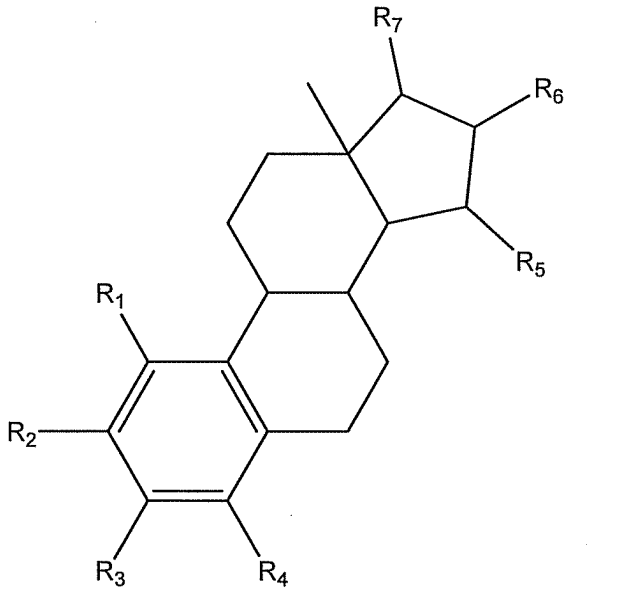
REJECTION UNDER 35 U.S.C. §103(A)

Claims 18-27 are rejected under 35 U.S.C. §103(a) as being unpatentable over United States Publication No. 2002/0183299 A1 to Voskuhl ("Voskuhl") in view of United States Patent No. 5,340,584 to Spicer *et al.* ("Spicer"). It is the Examiner's position that it would have been obvious to combine the method of Voskuhl for treating multiple sclerosis,

which is an autoimmune mediated disease, by administering an estrogenic hormone, such as estriol or a metabolite of estriol in view of the teachings of Spicer. Applicants respectfully traverse this rejection.

The Claimed Invention

The invention, as recited in claims 18, is a method of treating or prophylactically treating an immune mediated disorder in a mammal. The method comprises administering a therapeutically effective amount of an estrogenic component having a formula selected from the group consisting of:



in which formula R_1, R_2, R_3, R_4 independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms; precursors capable of liberating a substance according to the aforementioned formula, which precursors are derivatives of the estrogenic substances wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue; and mixtures of one or more of the aforementioned

substances and/or precursors. In one embodiment, the estrogenic component is estetrol. Claims 19-27 and new claim 34 ultimately depend from claim 18.

The Cited References

Voskuhl teaches a method of treating an autoimmune disease, more specifically a Th-1 mediated autoimmune disease, such as multiple sclerosis, by administering at least one primary agent being an estrogen or estrogen receptor active agent. The examples in the reference describe a study in which women with clinically definite multiple sclerosis were treated with estriol. Paragraph 39 of the reference states that the primary agent may also be a metabolite or derivative of E_1, E_2, or E_3, which are active at the estrogen receptor α or β. The reference further states that metabolites and derivatives may have a similar core structure to E_1, E_2, or E_3, but may have one or more different groups, i.e., hydroxyl, ketone, halide, etc., at one or more ring positions.

Spicer is directed to a contraceptive composition comprising a slow-release formulation of a gonadotropin releasing hormone composition, a slow-release formulation of an estrogenic hormone, and a slow-release formulation of a progestogen. The natural and synthetic estrogenic compositions discussed in Spicer "include natural estrogenic hormones and congeners, including but not limited to estradiol, ... ethinyl estradiol, ... estriol .... Equine estrogens, such as equilelinin, equilelinin sulfate and estetrol, may also be employed."[5]

According to the Office Action, Voskuhl does not explicitly teach estetrol as a primary agent used in a method of treating or preventing autoimmune mediated disease.[6] However, the Examiner asserts that since Spicer teaches that estriol and estetrol are functionally equivalent natural estrogen hormones that can be used interchangeably, it would have been obvious to employ estetrol in the method of treating or preventing an autoimmune mediated disease taught by Voskuhl.[7] The Office Action additionally states: "[f]urthermore, if such a species or subgenus is structurally similar to that claimed, such as estriol and estetrol in this

[5] Spicer at column 5, lines 51-61.

[6] Office Action of August 9, 2007 at page 17.

[7] Office Action of August 9, 2007 at pages 16-17.

instant, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties."[8]

Previous Arguments

As discussed on pages 4-5 of the present application, available knowledge of the pharmacological properties of estetrol, at the time the present invention was made, clearly shows that estetrol is a much less potent estrogen than the natural estrogens estradiol and estriol. For instance, Levine *et al.*, "Uterine vascular effects of estetrol in nonpregnant ewes," AM. J. OBSTET. GYNECOL., (1984) 148(73): 735-738 observe: "When intravenously administered in nonpregnant ewes, estetrol is 15 to 30 times less potent than estriol and 17β-estradiol in uterine vasodilation."

Indeed, until the date of the present invention, as far as Applicants are aware, there is no record of any actual therapeutic use of estetrol. In a few patent publications (such as Spicer) estetrol is mentioned; however, none of these references actually illustrates the therapeutic use of estetrol.

Consequently, Applicants respectfully traverse the position that one skilled in the art having adequate knowledge in the field of steroids would conclude from Spicer that estriol and estetrol can be used interchangeably. Rather, it is Applicants' position that one having ordinary skill in the art would attach much more relevance to the available scientific literature showing that estetrol has very limited estrogenic activity than to patent publications in which estetrol is presented as an estrogen that may be used in a therapeutic method without there being provided any data to corroborate this "suggestion".

Accordingly, one having ordinary skill in the art would ***not*** be motivated to combine the teachings of Voskuhl with those of Spicer since these references related to very different fields (autoimmune diseases versus contraception and gynecological disorders) and also because a skilled person looking for alternative estrogenic agents besides those explicitly

[8] Office Action of August 9, 2007 at page 17.

mentioned in Voskuhl would find little guidance in Spicer. In addition, it is Applicants' position that even if a skilled person would try to combine the teachings of Voskuhl with those of Spicer, such skilled person would ***not*** be motivated by Spicer to use estetrol in the method of treating immune diseases described in Voskuhl because this skilled person, based on the available knowledge of estetrol, would not expect that estetrol could successfully be used in such a method. Thus, it is only with the benefit of hindsight that one can argue that a skilled person would have been motivated by Spicer to employ estetrol as the primary agent in the method of treating autoimmune disease of Voskuhl.

Further Arguments

Further and in addition to the reasons discussed above, the recited invention is patentable over the cited references because a *prima facie* case of obviousness has not been established, and because it was unexpected that estetrol would be pharmacologically active. The Office Action does not explain why one would reasonably expect to successfully use estetrol when the prior art actually describing pharmacological properties of estetrol teaches that estetrol was not pharmacologically active. Further, the unexpected result establishes that the recited invention is patentable over the cited references.

I. There is no reasonable expectation of successfully using estetrol in the recited method.

Prior to the disclosure of the present invention, estetrol was believed to be a very weak natural estrogen.[9] In fact, a person of ordinary skill in the art believed that estetrol would not have any meaningful pharmacological effect due to its low estrogenic potency, and the fact that one would have expected estetrol to be similar to the natural estrogens estradiol and estriol in exhibiting a very short elimination half-life. The specification identifies several references that establish estetrol's low receptor binding affinity and poor estrogenicity:

- Levine et al., 1984. Uterine vascular effects of estetrol in non-pregnant ewes. Am. J. Obstet. Gynecol., 148:73, 735-738: "When intravenously administered in non-pregnant ewes, estetrol is 15 to 30 times less potent than estriol and 17.beta.-estradiol in uterine vasodilation".

[9] See Holinka (1980), abstract.

- Jozan et al., 1981. Different effects of oestradiol, oestriol, oestetrol and of oestrone on human breast cancer cells (MCF-7) in long term tissue culture. Acta Endocrinologica, 98, 73-80: "Estetrol agonistic potency is 2% of the magnitude observed for 17β-estradiol in in-vitro cell proliferation".
- Holinka et al., 1980. Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on the immature rat uterus. Biol. Reprod. 22, 913-926: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17β-estradiol and estriol".
- Holinka et al., 1979. In vivo effects of estetrol on the immature rat uterus. Biol. Reprod. 20, 242-246: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17β-estradiol and estriol".
- Tseng et al., 1978. Heterogeneity of saturable estradiol binding sites in nuclei of human endometrium. Estetrol studies. J. Steroid Biochem. 9, 1145-1148: "Relative binding of estetrol to estrogen receptors in the human endometrium is 1.5% of 17β-estradiol".
- Martucci et al., 1977. Direction of estradiol metabolism as a control of its hormonal action-uterotrophic activity of estradiol metabolites. Endocrin. 101, 1709-1715: "Continuous administration of estetrol from a subcutaneous depot shows very weak uterotrophic activity and is considerably less potent than 17.beta.-estradiol and estriol".
- Tseng et al., 1976. Competition of estetrol and ethynylestradiol with estradiol for nuclear binding in human endometrium. J. Steroid Biochem. 7, 817-822: "The relative binding constant of estetrol binding to the estrogen receptor in the human endometrium is 6.25% compared to 17β-estradiol (100%)".
- Martucci et al., 1976. Uterine estrogen receptor binding of catecholestrogens and of estetrol (1,3,5(10)-estratriene-3,15alpha,16alph, 17beta-tetrol). Steroids, 27, 325-333: "Relative binding affinity of estetrol to rat uterine cytosol estrogen receptor is 0.5% of 17β-estradiol (100%). Furthermore, the relative binding affinity of estetrol to rat uterine nuclear estrogen receptor is 0.3% of 17β-estradiol (100%)".[10]

To further evidence these points, Applicants submit declarations from third-party artisans in the field, and a declaration from one of the co-inventors. As these declarations establish, prior to the publication of this invention, one of ordinary skill in the art believed that

[10] Specification at pages 4-5. Copies of these references were previously submitted with the Information Disclosure Statement of August 8, 2005.

estetrol would not have been pharmacologically active.[11] This is because it was known in the art that estetrol had a substantially lower receptor affinity than estradiol or estriol.[12] Specifically, one of ordinary skill would have expected estetrol to be less effective than estradiol or estriol because the Holinka article (1980)[13] suggests that estetrol is a much weaker estrogen than the already weak estrogen estriol, given that estetrol injected subcutaneous at 50 μg/100 g body mass exhibited less estrogenic activity than estriol injected subcutaneous at 1 μg/100 g body mass.[14] Estriol is a very weak estrogen due to its low receptor affinity in combination with its very short half-life of 5-10 minutes.[15] Since Holinka teaches that estrogenic activity of estetrol is at least 50 times lower than that of a weak estrogen for which very few practical applications exists, Holinka would not have provided a motivation for a person of ordinary skill in the art to further investigate the potential pharmacological usefulness of estetrol.[16] Instead, this article teaches away from estetrol having any significant pharmacological effect.

Additionally, a person of ordinary skill in the art would have expected estetrol to be comparable to estriol.[17] Estetrol differs from estriol by only one hydroxyl group, and both estriol and estetrol are produced during pregnancy.[18] Hence, one of ordinary skill in the art would have believed that estetrol, like estriol, has a very short half-life on the order of minutes.[19]

Thus, the recited invention is patentable over the cited references because one of ordinary skill in the art would not reasonably expect that he or she could successfully use estetrol

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[11] See Declaration by Strauss at ¶¶ 8-9; see also Declaration by Speroff at ¶¶ 8-9; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[12] See Holinka (1980), abstract, see also Declaration by Strauss at ¶¶ 15-16, 18 and 20; see also Declaration by Speroff at ¶¶ 15-16, 18 and 20; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[13] Holinka et al., "Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on immature rat uterus, "BIOL. OF REPROD., (1980) 22(4): 913-926. A copy was previously provided with the Information Disclosure Statement of August 8, 2005.

[14] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; Declaration by Coelingh Bennink at ¶¶ 5.

[15] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; Declaration by Coelingh Bennink at ¶¶ 5.

[16] Declaration by Strauss at ¶¶ 15-16; Declaration by Speroff at ¶¶ 15-16; Holinka (1979); and Holinka (1980).

[17] Declaration by Strauss at ¶ 1; and Declaration by Speroff at ¶ 18.

[18] Declaration by Strauss at ¶ 1; and Declaration by Speroff at ¶ 18.

[19] Declaration by Strauss at ¶ 1; and Declaration by Speroff at ¶ 18.

since it was believed that estetrol was not pharmacologically active. When making a rejection under 35 U.S.C. § 103, the examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 131 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However, the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases. *Id.* at

2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream of catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'coventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an appropriate location for the adsorbent catalyst 16 in the apparatus of Swaroop ...." *Id.* at 5-6. The Board held that

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. ... Fourth, the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Emphasis added, *Ikeda*, App. No. 08/352,079 at 7.

Following the reasoning stated in *Takeda Chemical* and *Ikeda*, the Office Action must provide some explanation why one of ordinary skill in the art would believe that estetrol would be pharmacologically active when estetrol was believed to have too little estrogenic potency to be useful. As discussed above, prior to the publication of this invention, one of ordinary skill in the art would not expect estetrol to be pharmacologically active because it was known that estetrol was a considerably weaker estrogen than the already weak estrogen estriol.

It was not until the Applicants discovered estetrol's very long terminal elimination half-life that it became apparent that estetrol could be pharmacologically active. Prior to the disclosure of this invention, there was no publicly available data about the terminal elimination half-life of estetrol, about estetrol's binding to SHBG or about estetrol's effect on SHBG production.[20] Since estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes, respectively, it was believed that estetrol, another natural estrogen, would likewise have a short, if not shorter, terminal elimination half-life.[21] Unexpectedly, the Applicants discovered that estetrol has a terminal elimination half-life of about 28 hours.[22]

> A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone estriol, was very unexpected and provided the clue towards its pharmacological usefulness.[23]

Like *Takeda Chemical*, one of ordinary skill in the art would have had no reason to use estetrol because it was believed not to be pharmacologically active. Maintaining a rejection based on the premise that estetrol can be used instead of estrone (E_1), estradiol (E_2) or estriol (E_3) is improper for the same reasons that the rejection in *Ikeda* was improper – because the prior art teaches away from using estetrol. As part of a *prima facie* case of obviousness, there must be some explanation why one of ordinary skill in the art would consider using estetrol when the prior art teaches that it is not pharmacologically active. Since such an explanation has not been provided, a *prima facie* case of obviousness has not been established. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

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[20] Declaration by Coelingh Bennink at ¶¶ 4.

[21] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[22] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[23] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

II. It was unexpected to discover that estetrol is useful in the recited method.

Additionally, the unexpected result that estetrol is pharmacologically active because it has a long terminal elimination half-life rebuts the obviousness rejection. See *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311, 79 U.S.P.Q.2d 1931 (Fed. Cir. 2006); see also *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). To establish unexpected results, the Applicant must "establish (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art, *In re Klosak*, 455 F.2d 1077, 59 CCPA 862 (1972); and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention, *Id.*; *In re D'Ancicco*, 439 F.2d 1244, 58 CCPA 1057 (1971)." *In re Freeman*, 474 F.2d 1318, 1324 (CCPA 1973). Without evidence to the contrary, an applicant need only provide substantially improved results and state that the results were unexpected. *Soni*, 54 F.3d at 750; *In re Lee*, App No. 10/091,061, 2007 WL 176690 at *3 (BPAI June 19, 2007).

In *Soni*, the examiner rejected certain claims as obvious in view of a combination of references. The applicant directed the examiner to the data in the specification, and argued that the increase in tensile strength and the increase in peel strength rebutted the rejections. *Soni*, 54 F.3d at 747. On appeal to the Federal Circuit, it was argued that the Board "could have taken judicial notice of the fact that higher molecular weight polymers would have been expected to tolerate higher filler loadings without degradation in properties and that it could have taken notice of the fact that it is the polymer *per se* that primarily determines the mechanical properties of a filled polymer composition." *Id.* at 750. However, the Federal Circuit found this argument fatally flawed because the Board failed to support its position with facts or evidence. *Id.* at 750; see also *Lee*, 2007 WL 176690 at *3. In summary, the Federal Circuit held that "[m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected,* this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, 54 F.3d at 751.

Estetrol has a terminal elimination half-life of 28 hours, which is 168-336 times greater than estriol's terminal half-life and about 56 times greater than estradiol's terminal half-life. [24] Thus, there is an actual difference and substantial improvement between estetrol and estriol as well as between estetrol and estradiol.

One of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only one hydroxyl group and from estradiol by two hydroxyl groups and (ii) both estriol and estetrol are produced during pregnancy.[25] Thus, one of ordinary skill in the art would have expected estetrol to have a terminal elimination half-life similar to estriol – on the order of a few minutes.[26] Unexpectedly, the Applicants discovered that estetrol's terminal elimination half-life was 28 hours.

The unexpectedly long terminal elimination half-life is associated with the unexpected pharmacological activity of estetrol. As discussed above, estetrol was known to be a very weak estrogen, so much so that it was dismissed by those of ordinary skill in the art as not being pharmacologically active.[27] Thus, it was unexpected to discover that estetrol, due to its unexpectedly long terminal elimination half-life, would be pharmacologically active.

Therefore, even assuming that a *prima facie* case of obviousness has been established, the unexpected results – that estetrol has an unexpectedly long terminal elimination half-life, and/or that estetrol is pharmacologically active – provide evidence that the recited invention is patentable over the cited references.

III. <u>There is no reasonable expectation of successfully using estetrol in oral applications.</u>

New claim 34 is directed to the method recited in claim 18 wherein the estrogenic component is administered ***orally***. Prior to the disclosure of this invention, a person of ordinary

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[24] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[25] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[26] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[27] Declaration by Coelingh Bennink at Exhibit B.

skill in the art expected estetrol to be similar to the natural estrogens estradiol and estriol in exhibiting a very short elimination half-life and very low oral bioavailability.[28] Estradiol, estriol and estrone exhibit low oral bioavailability because they are largely metabolized into inactive metabolites during the so called "first pass" through the liver after oral administration.[29] Given that estetrol's estrogen receptor affinity was known to be considerably lower than that of estradiol and estriol, a person of ordinary skill in the art, being aware that known human estrogens are largely metabolized during the first pass, would have expected to find that estetrol likewise has low oral bioavailability.[30] However, the Applicants unexpectedly discovered that estetrol has a very high oral bioavailability.[31]

In order to establish a *prima facie* case of obviousness, the Office Action must provide some reason why a person of ordinary skill in the art would consider estetrol to be pharmacologically active when orally administered in view of the fact that other natural estrogens were known to be quickly metabolized into inactive metabolites following oral administration and in view of the fact that estetrol's estrogenic potency was known to be considerably lower than that of estradiol and estriol. Since such a reason has not been provided, a *prima facie* case of obviousness with regard to new claim 34 cannot be established.

IV. It was unexpected to discover that estetrol is useful in oral applications

Moreover, it was unexpected that estetrol is pharmacologically active when orally administered.[32] According to the prior art, estriol has a very low oral bioavailability as it is metabolized very rapidly.[33] One of ordinary skill in the art would have expected estetrol to have similar oral bioavailability as estriol because both are natural estrogens differing by only one hydroxyl group.[34] Thus, it was unexpected to discover the high oral bioavailability of estetrol

[28] Declaration by Strauss at ¶ 7; and Declaration by Speroff at ¶ 7.

[29] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[30] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[31] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[32] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[33] Declaration by Strauss at ¶ 18; and Declaration by Speroff at ¶ 18.

[34] Declaration by Strauss at ¶ 17; and Declaration by Speroff at ¶ 17.

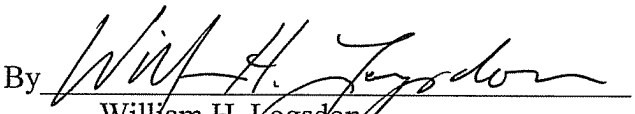
because, prior to the disclosure of the invention, there was no reason for a person of ordinary skill in the art to believe that estetrol was orally bioavailable.[35] Due to these unexpected results, the invention as recited in new claim 34 is patentable over the cited references.

CONCLUSION

Accordingly, Applicants respectfully request that the asserted rejections be reconsidered and withdrawn, and that claims 18-27 and 34 be allowed.

Respectfully submitted,

The Webb Law Firm

By 

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[35] Declaration by Strauss at ¶ 7; and Declaration by Speroff at ¶ 7.